



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07C 237/06, A61K 31/16, C07C 321/30		A1	(11) International Publication Number: WO 97/05102
		(43) International Publication Date: 13 February 1997 (13.02.97)	
(21) International Application Number: PCT/EP96/02961 (22) International Filing Date: 5 July 1996 (05.07.96) (30) Priority Data: 9515412.6 27 July 1995 (27.07.95) GB (71) Applicant (for all designated States except US): PHARMACIA & UPIOHN S.P.A. [IT/IT]; Via Robert Koch, 1.2, I-20152 Milan (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): PEVARELLO, Paolo [IT/IT]; Piazza San Pietro in Ciel d'Oro, 7/A, I-27100 Pavia (IT). AMICI, Raffaella [IT/IT]; Via N. Rocca, 11, I-29100 Piacenza (IT). VARASI, Mario [IT/IT]; Via Giambellino, 80, I-20146 Milan (IT). BONSIGNORI, Alberio [IT/IT]; Via dei Benedettini, 2, I-20146 Milan (IT). SALVATI, Patricia [IT/IT]; Via Valesa, 16/C, I-20020 Arese (IT).		(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, DE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.	
(54) Title: 2-(4-SUBSTITUTED)-BENZYLAMINO-2-METHYL-PROPANAMIDE DERIVATIVES			
(57) Abstract Novel 2-(4-substituted)-benzylamino-2-methyl-propanamides compounds, having CNS activity, of general formula (I) wherein: n is zero, 1, 2 or 3; X is -O-, -S-, -CH2- or -NH-; each of R and R ₁ independently is hydrogen, C ₁ -C ₆ alkyl, halogen, hydroxy, C ₁ -C ₄ alkoxy or trifluoromethyl; each of R ₂ , R ₃ and R ₄ independently is hydrogen, C ₁ -C ₆ alkyl or C ₃ -C ₇ cycloalkyl; and the pharmaceutically acceptable salts thereof, are disclosed.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LT	Lithuania	SN	Senegal
CN	China	LU	Luxembourg	SZ	Swaziland
CS	Czechoslovakia	LV	Latvia	TD	Chad
CZ	Czech Republic	MC	Monaco	TG	Togo
DE	Germany	MD	Republic of Moldova	TJ	Tajikistan
DK	Denmark	MG	Madagascar	TT	Trinidad and Tobago
EE	Estonia	ML	Mali	UA	Ukraine
ES	Spain	MN	Mongolia	UG	Uganda
FI	Finland	MR	Mauritania	US	United States of America
FR	France			UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

**2-(4-SUBSTITUTED)-BENZYLAMINO-2-METHYL-PROPANAMIDE
DERIVATIVES**

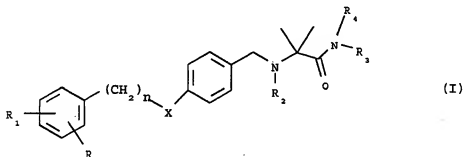
The present invention relates to novel 2-(4-substituted)-
5 benzylamino-2-methyl-propanamides, to their use as
therapeutic agents, to a process for their preparation and to
pharmaceutically compositions containing them.

WO 90/14334 discloses N-phenylalkyl substituted α -amino
carboxamide derivatives active on the CNS.

10 It has been found that novel 2-(4-substituted)-benzylamino-2-
methyl-propanamides derivatives as herein defined have
valuable biological properties, in particular as
antiepileptic, anti-Parkinson, neuroprotective, anti-
depressant, antispastic and/or hypnotic agent.

15

The present invention provides novel compounds of the
following general formula (I)



wherein:

20 n is zero, 1, 2 or 3;

X is -O-, -S-, -CH₂- or -NH-;

each of R and R₁ independently is hydrogen, C₁-C₆ alkyl,
halogen, hydroxy, C₁-C₄ alkoxy or trifluoromethyl;

each of R₂, R₃ and R₄ independently is hydrogen, C₁-C₆ alkyl
25 or C₃-C₇ cycloalkyl;

and the pharmaceutically acceptable salts thereof.

The pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts with inorganic, e.g. hydrochloric, hydrobromic, sulfuric, and phosphoric acids, or organic, e.g. acetic, propionic, lactic, oxalic, malic, maleic, tartaric, citric, benzoic, mandelic, C₁-C₄ alkylsulfonic, salicylic and fumaric acids.

The compounds of the formula (I), their pharmaceutically acceptable salts may also form pharmaceutically acceptable solvates, such as mono-, di- or tri-hydrates, which are also object of the present invention.

The alkyl and alkoxy groups may be branched or straight groups.

A C₁-C₆ alkyl group is preferably a C₁-C₄ alkyl group, in particular methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl, more preferably methyl or ethyl.

Representative examples of C₁-C₄ alkoxy groups include methoxy or ethoxy.

A halogen atom is e.g. chlorine, fluorine or bromine.

A C₃-C₇ cycloalkyl group is, for instance, a cyclopropyl, cyclohexyl or cycloheptyl group, in particular cyclopropyl.

The present invention also include within its scope all the possible isomers of the compounds of formula (I) and their mixtures, as well as the metabolites and the pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

Preferred compounds of the invention are the compounds of formula (I) wherein

n is 1 or 2;

X is -O-, -S- or -NH-;

R is hydrogen;

R₁ is hydrogen or halogen;

each of R_2 , R_3 and R_4 independently is hydrogen or C_1 - C_4 alkyl; and the pharmaceutically acceptable salts thereof.

More preferred compounds of the invention are the compounds
5 of formula (I), wherein

n is 1;

X is -O-, -S- or -NH-;

R_1 is hydrogen or halogen;

R , R_2 , R_3 and R_4 are hydrogen; and the pharmaceutically
10 acceptable salts thereof.

Examples of specific compounds of the invention are:

2-[4-(3-fluorobenzyloxy)benzylamino]-2-methyl-propanamide;

2-[4-(3-chlorobenzyloxy)benzylamino]-2-methyl-propanamide;

15 2-[4-(4-chlorobenzyloxy)benzylamino]-2-methyl-propanamide;

2-[4-(3-bromobenzyloxy)benzylamino]-2-methyl-propanamide;

2-[4-(4-fluorobenzyloxy)benzylamino]-2-methyl-propanamide;

2-[4-(2-fluorobenzyloxy)benzylamino]-2-methyl-propanamide;

2-[4-(3-fluorobenzylamino)benzylamino]-2-methyl-propanamide;

20 2-[4-(benzylsulfanyl)benzylamino]-2-methyl-propanamide;

2-[4-(3-fluorobenzyloxy)benzylmethylamino]-2-methyl-
propanamide;

2-{[4-(3-fluorobenzyloxy)benzyl]-amino}-2-methyl-N-methyl-
propanamide;

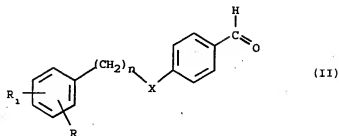
25 2-{[4-(3-chlorobenzyloxy)benzyl]methylamino}-2-methyl-
propanamide; and

2-{[4-(3-bromobenzyloxy)benzyl]methylamino}-2-methyl-
propanamide, if the case, either as single (S) or (R) isomer
or as a mixture thereof, and the pharmaceutically acceptable
30 salts thereof.

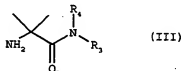
The compounds of the invention and the salts thereof can be

obtained by a process comprising:

- a) reacting a compound of formula (II)

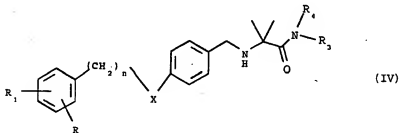


- 5 wherein n , R , R_1 and X are as defined above, with a compound of formula (III)



wherein R_3 and R_4 are as defined above, thus obtaining a compound of formula (I) in which R_2 is hydrogen; or

- 10 b) reacting a compound of formula (IV)



wherein R , R_1 , R_3 , R_4 , n and X are as defined above, with a compound of formula (V) or (VI)

- 15 R'_2W (V) R'_2CHO (VI)

wherein W is a halogen atom; R'_2 is a C_1 - C_6 alkyl and R'_2 is hydrogen or C_1 - C_5 alkyl, thus obtaining a compound of the invention in which R_2 is C_1 - C_6 alkyl; and, if desired, converting a compound of the invention into another compound of the invention and/or, if desired, converting a compound of the invention into a

pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound.

All the processes described hereabove are analogy processes and can be carried out according to well known methods in organic chemistry.

A compound of formula (IV) is a compound of formula (I) in which R_2 is hydrogen.

The reaction of a compound of formula (II) with a compound of formula (III) to give a compound of formula (I) or (IV) is a reductive amination reaction which can be carried out according to well known methods. According to a preferred embodiment of the invention it may be performed under nitrogen atmosphere, in a suitable organic solvent, such as an alcohol, e.g. a lower alkanol, in particular methanol, or in acetonitrile, at a temperature ranging from about 0°C to about 40°C, in the presence of a reducing agent, the most appropriate being sodium cyanoborohydride. Occasionally molecular sieves can be added to the reaction mixture for facilitating the reaction.

In a compound of formula (V) the halogen W is preferably iodine. The alkylation reaction of a compound of formula (IV) with a compound of formula (V) can be carried out in a suitable organic solvent, such as an alcohol, e.g. methanol, ethanol or isopropanol, in particular in ethanol, at a temperature ranging from about 0°C to about 50°C.

The alkylation reaction of a compound of formula (IV) with an aldehyde of formula (VI) can be carried out in a suitable organic solvent, such as an alcohol, e.g. methanol, ethanol or acetonitrile in the presence of a suitable reducing agent, such as sodium cyanoborohydride, at a temperature ranging from about 0°C to about 30°C.

A compound of the invention can be converted, as stated above, into another compound of the invention by known methods. Process-variant b) above may be regarded as an example of optional conversion of a compound of the invention into another compound of the invention.

Also the optional salification of a compound of the invention as well as the conversion of a salt into the free compound may be carried out by conventional methods.

The compounds of formula (II), (III), (V) and (VI) are known compounds or can be obtained by known methods.

When in the compounds of the present invention and in the intermediate-products thereof, groups are present, which need to be protected before submitting them to the hereabove illustrated reactions, they may be protected before being reacted and then deprotected according to methods well known in organic chemistry.

PHARMACOLOGY

The compounds of the invention are active on the central nervous system (CNS) and can be used in therapy, for example as antiepileptics, in the treatment of Parkinson's disease and as neuroprotective agents, e.g. preventing or treating neuronal loss associated with stroke, hypoxia, ischemia, CNS trauma, hypoglycaemia or surgery and in treating and preventing neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis, Down's syndrome, Huntington's disease, dementia caused by acquired immunodeficiency syndrome (AIDS), infarctual dementia and infections or inflammations in the brain; they can also be used as antidepressants, hypnotics and antispastic agents and in treating ocular damage and rethinopathy.

The activity on the CNS of the compounds of the invention was

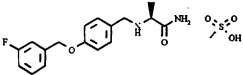
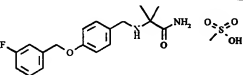
evaluated on the basis of pharmacological methods, such as, for example, the antagonism of convulsions and lethality induced by intravenous injection of bicuculline in mice (Antiepileptic Drugs, D.M. Woodbury et al. eds., 2nd edition, Raven Press, New York, 1982), or the antagonism of maximal electroshock seizures (MES) (Woodbury, L.A. and Davenport, V.D., Arch. Int. Pharmacodyn. Ther. 92; 97-104, 1952).

The following table summarizes the activity data obtained by testing in the MES test a representative group of compounds of the invention in comparison with the respective 2-desmethyl related compounds known from WO 90/14334.

The symbol * identifies the prior art 2-desmethyl-compounds known from WO 90/14334.

ED₅₀ means effective dose in 50% of treated animals after per os (po) administration.

Table 1

Structure	Compound (internal code)	MES-ED ₅₀ (po) mg/Kg
	FCE 26743A*	8.2 (7.2-9.4)
	FCE 29088A	4.4 (2.8-6.3)

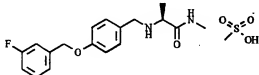
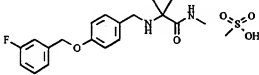
(cont...)

Table 1 (cont'd)

Structure	Compound (internal code)	MES-ED ₅₀ (po) mg/Kg
	FCE 26727A*	12.72 (9.19-17.62)
	FCE 29482A	3.12 (2.28-4.27)
	FCE 26742A*	7.13 (5.70-8.91)
	FCE 29484A	3.10 (2.25-4.28)
	FCE 26193A*	9.41 (7.12-12.4)
	FCE 29644A	3.88 (2.90-5.19)
	FCE 26998A*	16.30 (7.18-37.12)
	FCE 29645A	6.58 (4.02-16.97)

(cont..)

Table 1 (cont'd)

Structure	Compound (internal code)	MES-ED ₅₀ (po) mg/Kg
	FCE 28657A*	9.35 (4.34-13.11)
	FCE 29647A	4.34 (3.28-5.75)

where internal code:

- FCE 29088A means 2-(4-(3-fluorobenzoyloxy)benzylamino)-2-methyl-propanamide, methanesulfonate;
- 5 FCE 26743A* means (S)-2-(4-(3-fluorobenzoyloxy)benzylamino)propanamide, methanesulfonate;
- FCE 29482A means 2-(4-benzylsulfanyl)benzylamino)-2-methyl-propanamide, methanesulfonate;
- 10 FCE 26727A* means (S)-2-(4-benzylsulfanyl)benzylamino)propanamide, methanesulfonate;
- FCE 29484A means 2-(4-(2-fluorobenzoyloxy)benzylamino)-2-methyl-propanamide, methanesulfonate;
- FCE 26742A* means (S)-2-(4-(2-fluorobenzoyloxy)benzylamino)propanamide, methanesulfonate;
- 15 FCE 29644A means 2-(4-(3-chlorobenzoyloxy)benzylamino)-2-methyl-propanamide, methanesulfonate;
- FCE 26193A* means (S)-2-(4-(3-chlorobenzoyloxy)benzylamino)propanamide, methanesulfonate;
- 20 FCE 29645A means 2-(4-(4-fluorobenzoyloxy)benzylamino)-2-methyl-propanamide, methanesulfonate;
- FCE 26998A* means (S)-2-(4-(4-fluorobenzoyloxy)benzylamino)propanamide, methanesulfonate;

FCE 29647A means 2-(4-(3-fluorobenzoyloxy)benzylamino)-2-methyl-N-methylpropanamide, methanesulfonate;

FCE 28657A* means (S)-2-(4-(3-fluorobenzoyloxy)benzylamino)-N-methylpropanamide, methanesulfonate.

5

The comparative activity test data set out in the above table show that the new compounds of the instant invention are from 2 to 4 fold more active than the closely related prior art compounds.

- 10 A patient is treated according to the present invention by a method comprising administering to the patient an effective amount of one of the compounds of the invention. In this way the present compounds can be used to treat disorders of the central nervous system, for example epilepsy or Parkinson's
- 15 disease; or as neuroprotective agents, anti-depressants, hypnotics or anti-spastic agents. The condition of a patient may thus be improved.

The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets,

20 capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous injection or infusion.

The dosage depends on the age, weight, conditions of the

25 patient and on the administration route; for example, the dosage adopted for oral administration to adult humans e.g. for the representative compound of the invention 2-[4-(3-fluorobenzoyloxy)benzylamino]-2-methyl-propanamide may range from about 1 to about 500 mg pro dose, from 1 to 5 times

30 daily.

The invention includes pharmaceutical compositions comprising a compound of the invention, as an active principle, in

association with a pharmaceutically acceptable excipient (which can be a carrier or a diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, destrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

The liquid dispersion for oral administration may be e.g. syrups, emulsions and suspension.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

The suspension and the emulsion may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a

pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusion may contain
5 as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa
10 butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The following examples illustrate but do not limit the invention.

15 Example 1

2-[4-(3-fluorobenzoyloxy)benzylamino]-2-methyl-propanamide, methanesulfonate (FCE 29088A)

To a solution of 2-amino-2-methylpropanamide, hydrochloride
20 (7.01 g; 0.051 mol) in anhydrous methanol (160 ml), under stirring and nitrogen, 7.0 g of 3Å molecular sieves were added and then, in a single portion, NaBH_3CN (2.31 g; 0.037 mol), after 10 minutes, 10.6 g (0.046 mol) of 4-(3-fluorobenzoyloxy) benzaldehyde were added, in 140 ml of
25 anhydrous methanol. After 24 hours the reaction was completed, the mixture filtered, the solution was evaporated to give a residue which was directly flash-chromatographed on silica gel (eluant: CHCl_3 98: CH_3OH 2: 30% NH_4OH 0.15) to afford a white solid (6.2 g; 43%). The free base thus
30 obtained was treated with a stoichiometric amount of methanesulfonic acid to yield the title compound (m.p. 209-213°C).

Analogously, the following products can be obtained, starting from the corresponding aldehyde and the appropriate amide:

- 2-[4-(3-chlorobenzoyloxy)benzylamino]-2-methyl-propanamide,
methanesulfonate, m.p. 202-206°C (FCE 29644A);
- 2-[4-(3-bromobenzoyloxy)benzylamino]-2-methyl-propanamide,
methanesulfonate, m.p. 197-202°C (FCE 29494A);
- 2-[4-(4-fluorobenzoyloxy)benzylamino]-2-methyl-propanamide,
methanesulfonate, m.p. 233°C (FCE 29645A);
- 2-[4-(2-fluorobenzoyloxy)benzylamino]-2-methyl-propanamide,
methanesulfonate, m.p. 215-220°C (FCE 29484A);
- 2-[4-(3-fluorobenzylamino)benzylamino]-2-methyl-propanamide,
dihydrochloride, m.p. 165° ca. (dec.) (FCE 29822A);
- 2-[(4-benzylsulfanyl)benzylamino]-2-methyl-propanamide,
methanesulfonate, m.p. 214-215°C (FCE 29482A);
- 2-[4-(3-fluorobenzoyloxy)benzylamino]-2-methyl-N-methyl-
propanamide, methanesulfonate, m.p. 213-218°C (FCE 29647A);
and
- 2-[4-(4-chlorobenzoyloxy)benzylamino]-2-methyl-propanamide,
m.p. 226-227°C (FCE 29485A).

Example 2

2-[[4-(3-fluorobenzoyloxy)benzyl]methylamino]-2-methyl-
propanamide (FCE 29486)

25

- One g. (0.00316 mol) of 2-[(4-(3-fluorobenzoyloxy)benzylamino)-2-methyl-propanamide are dissolved in acetonitrile (50 ml) under a nitrogen stream. To this mixture, 3.16 ml (0.0389 mol) of 37% formaldehyde and 0.29 g
30 (0.00460 mol) of sodium cyanoborohydride are added at room temperature. After 20 minutes, glacial acetic acid is dropped

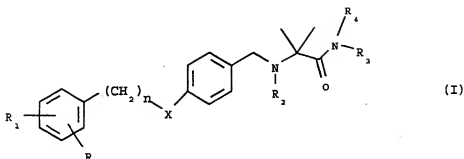
- up to neutrality of the solution. The mixture is stirred for 40 minutes and evaporated to dryness. 40 ml of 2N KOH are added to the residue. After extracting with ethyl acetate, washing with N/2 KOH and then with water and brine, the organic layer is dried on Na_2SO_4 , then filtered and evaporated to obtain a residue which is flash-chromatographed on silica gel (eluant: CHCl_3 200: CH_3OH 3: 30% NH_4OH 0.2) to give 0.75 (72%) of a white solid (m.p. 121-123°C).
- 10 Analogously the following products can be prepared starting from the corresponding secondary amine:
- 2-{{[4-(3-chlorobenzoyloxy)benzyl]methylamino}-2-methylpropanamide; and
- 2-{{[4-(3-bromobenzoyloxy)benzyl]methylamino}-2-methylpropanamide.
- 15

Example 3

- With the usual methods of pharmaceutical technique, preparation can be made of capsules having the following composition:
- 20
- | | |
|---|-------|
| 2-[4-(3-fluorobenzoyloxy)benzylamino]-2-methylpropanamide, methanesulfonate | 50 mg |
| Talc | 2 mg |
| Corn starch | 2 mg |
| 25 Microcristalline cellulose | 6 mg |
| Magnesium stearate | 1 mg |

CLAIMS

1. A compound of formula (I)



5 wherein:

n is zero, 1, 2 or 3;

X is -O-, -S-, -CH₂- or -NH-;

each of R and R₁ independently is hydrogen, C₁-C₆ alkyl, halogen, hydroxy, C₁-C₄ alkoxy or trifluoromethyl;

10 each of R₂, R₃ and R₄ independently is hydrogen, C₁-C₆ alkyl or C₃-C₇ cycloalkyl; or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I), according to claim 1,

15 wherein:

n is 1 or 2;

X is -O-, -S- or -NH-;

R is hydrogen;

R₁ is hydrogen or halogen;

20 each of R₂, R₃ and R₄ independently is hydrogen or C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof.

3. A compound of formula (I), according to claim 1,

wherein:

25 n is 1;

X is -O-, -S- or -NH-;

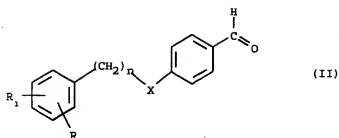
R₁ is hydrogen or halogen;

R, R₂, R₃ and R₄ are hydrogen; or a pharmaceutically acceptable salt thereof.

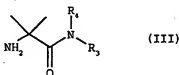
- 5 4. A compound selected from the group consisting of:
- 2-[4-(3-fluorobenzyloxy)benzylamino]-2-methyl-propanamide;
- 2-[4-(3-chlorobenzyloxy)benzylamino]-2-methyl-propanamide;
- 2-[4-(4-chlorobenzyloxy)benzylamino]-2-methyl-propanamide;
- 2-[4-(3-bromobenzyloxy)benzylamino]-2-methyl-propanamide;
- 10 2-[4-(4-fluorobenzyloxy)benzylamino]-2-methyl-propanamide;
- 2-[4-(2-fluorobenzyloxy)benzylamino]-2-methyl-propanamide;
- 2-[4-(3-fluorobenzylamino)benzylamino]-2-methyl-propanamide;
- 2-[4-(benzylsulfanyl)benzylamino]-2-methyl-propanamide;
- 2-[4-(3-fluorobenzyloxy)benzyl]-methylamino}-2-methyl-
- 15 propanamide;
- 2-[4-(3-fluorobenzyloxy)benzylamino]-2-methyl-N-methyl-
- propanamide;
- 2-{[4-(3-chlorobenzyloxy)benzyl]methylamino}-2-methyl-
- propanamide; and
- 20 2-{[4-(3-bromobenzyloxy)benzyl]methylamino}-2-methyl-
- propanamide, if the case, either as single (S) or (R) isomer
- or as a mixture thereof, or a pharmaceutically acceptable
- salt thereof.

- 25 5. A process for the preparation of a compound of
- formula (I), as defined in claim 1, or a pharmaceutically
- acceptable salt thereof, the process comprising:

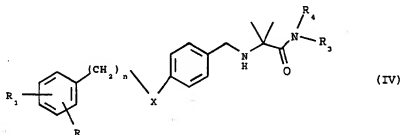
a) reacting a compound of formula (II)



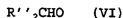
wherein n , R , R_1 and X are as defined in claim 1, with a compound of formula (III)



- 5 wherein R_3 and R_4 are as defined in claim 1, thus obtaining a compound of formula (I) in which R_2 is hydrogen; or
 b) reacting a compound of formula (IV)



- wherein R , R_1 , R_3 , R_4 , n and X are as defined in claim 1, with
 10 a compound of formula (V) or (VI)



- wherein W is a halogen atom; R'_2 is a C_1 - C_6 alkyl and R''_2 is hydrogen or C_1 - C_6 alkyl, thus obtaining a compound of the invention in which R_2 is C_1 - C_6 alkyl; and, if desired,
 15 converting a compound of the invention into another compound of the invention and/or, if desired, converting a compound of the invention into a pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound.

- 20 6. A pharmaceutical composition containing a suitable carrier and/or diluent and, as an active principle, a compound of

formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof.

7. A compound of formula (I), as defined in claim 1, or
5 a pharmaceutically acceptable salt thereof, for use as an active therapeutic substance.

8. A compound of formula (I), as defined in claim 1, or
a pharmaceutically acceptable salt thereof, for use as
10 antiepileptic agent, in the treatment of Parkinson's disease, as neuroprotective agent and in treating and preventing neurodegenerative diseases.

9. A compound of formula (I), as defined in claim 1, or
15 a pharmaceutically acceptable salt thereof, for use in treating ocular damage and rethinopathy.

10. A compound of formula (I), as defined in claim 1, or
a pharmaceutically acceptable salt thereof, for use as
20 antidepressant, hypnotic antispastic agent.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/EP 96/02961

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C237/06 A61K31/16 C07C321/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 90 14334 A (ERBA CARLO SPA) 29 November 1990 cited in the application see page 21; claims ---	
A	WO 94 22809 A (ERBA FARMITALIA) 13 October 1994 see claims; examples ---	
A	WO 94 22808 A (ERBA FARMITALIA) 13 October 1994 see claims; examples -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- 'A*' document member of the same patent family

Date of the actual completion of the international search

22 November 1996

Date of mailing of the international search report

29. 11. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2220 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Sánchez García, J.M.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/02961

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9014334	29-11-90	AU-B- 645752 AU-A- 5729990 CA-A- 2033190 CN-A, B 1047496 CZ-A- 9002520 DE-D- 69004337 DE-T- 69004337 EP-A- 0400495 EP-A- 0426816 ES-T- 2062174 IE-B- 63934 IL-A- 94466 JP-T- 4500215 NO-B- 179944 US-A- 5391577 US-A- 5502079 US-A- 5276611 US-A- 5236957	27-01-94 18-12-90 26-11-90 05-12-90 12-06-96 09-12-93 24-02-94 05-12-90 15-05-91 16-12-94 28-06-95 24-01-95 16-01-92 07-10-96 21-02-95 26-03-96 04-01-94 17-08-93
WO-A-9422809	13-10-94	AU-B- 667169 AU-A- 6377694 CA-A- 2136008 CN-A- 1104018 EP-A- 0648202 FI-A- 945582 HU-A- 70944 JP-T- 8504828 NZ-A- 263183 PL-A- 306538 US-A- 5449692 ZA-A- 9401964	07-03-96 24-10-94 13-10-94 21-06-95 19-04-95 28-11-94 28-11-95 28-05-96 27-02-96 03-04-95 12-09-95 19-10-94
WO-A-9422808	13-10-94	AU-B- 667164 AU-A- 6284294 CA-A- 2135783 CN-A- 1104017 EP-A- 0643688 FI-A- 945581 HU-A- 68256 JP-T- 7507814	07-03-96 24-10-94 13-10-94 21-06-95 22-03-95 28-11-94 28-06-95 31-08-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/02961

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9422808		NZ-A- 262907	27-02-96
		PL-A- 306537	03-04-95
		US-A- 5446066	29-08-95
		ZA-A- 9401963	19-10-94
